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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FOLEY HOAG, LLP
PATENT GROUP, WORLD TRADE CENTER WEST
155 SEAPORT BLVD
BOSTON, MA 02110

EXAMINER	
GAMBEL, PHILLIP	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/732,847	GRIBBEN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/27/06; 7/23/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *5,6 and 8-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of the species of "anti-B7-2 antibody as the second agent / blocking molecule" and "diabetes as the autoimmune disease" in the Reply to Restriction Requirement, filed 12/27/2006, has been acknowledged in the Office Action, mailed 03/22/2007.

Applicant's election with traverse of the species "wherein an autoantigen is not administered to the subject" the Reply to Restriction Requirement, filed 07/23/2007, is acknowledged.

The traversal is the extent that no undue burden would be required to search the encompassed species.

This is not found persuasive for the reasons of record set set forth in the Election of Species Requirement, mailed 07/23/2007.

The methods rely upon different ingredients, process steps and endpoints. Providing an autoantigen in addition to antagonistic antibodies provides another ingredient (i.e., autoantigen), which is distinct because its/their structure(s) and modes of action are different, which require non-coextensive searches. It is noted that these "autoantigen(s)" do not share a substantial structural feature essential to a common utility with anti-CTLA-4 antibodies or anti-B7-2 antibodies.

Also, the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph (e.g., written description and/or enablement of "administering an autoantigen for autoimmune disease:).

Therefore, they are patentably distinct.

Claims 1-14 are pending.

Claims 5-6 and 8-14 have been withdrawn as being drawn to non-elected inventions and/or species.

However, in the interest of compact prosecution,
examination in the instant application has been extended to include the other species of "administering to the subject at least one second agent that inhibits a costimulatory signal in the T cell", as it reads on "a blocking molecule that binds to a ligand selected from a group consisting of B7-1, By-2 and CD28 (e.g., see claims 3-4).

Claims 1-4 and 7 are being acted upon as they read upon the elected invention.

2. If applicant desires priority under 35 U.S.C. § 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. *If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application.* If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Benefit claims under 35 U.S.C. 120 must include a specific reference to the earlier filed (nonprovisional) application for which a benefit is sought. A "specific reference" requires: *(1) the identification of the prior (nonprovisional) application by application number; and (2) an indication of the relationship between the nonprovisional applications, except for the benefit claim to the prior application in a continued prosecution application (CPA). The relationship between any two nonprovisional applications will be an indication that the later-filed nonprovisional application is either a continuation, divisional, or continuation-in-part of the prior-filed nonprovisional application. When there are benefit claims to multiple prior nonprovisional applications (e.g., a string of prior nonprovisional applications), the relationship must include an identification of each nonprovisional application as either a continuation, divisional, or continuation-in-part application of a specific prior nonprovisional application for which a benefit is claimed.* The identification is needed in order to be able to verify if copendency exists throughout the entire chain of prior nonprovisional applications.

See United States Patent and Trademark Office OG Notices:
1268 OG 89 (18 March 2003).

Applicant should amend the first line of the specification to update the status of the priority documents.

In addition, applicant is required to indicate the proper relationship of this application to International Application No. PCT/US95/06726, filed June 2, 1995.

3. The effective filing date of the instant claim is deemed to be the filing date of the priority application USSN 08/253,783, filed 06/03/1994.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite in the recitation of "or fragment thereof" in that while applicant's intent may be directed to "antigen-binding fragments therefo / CTLA4-binding fragments thereof", the claims are no so limited and can read on any fragment. For example, immunoglobulin Fc fragments comprised immunoglobulin effector function capabilities and often employed in therapeutic agents; however this does not appear to be applicant's intent for the claimed invention herein.

The claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant is invited to amend the claims to recite the appropriate "fragments thereof".

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. This is a 35 U.S.C § 112, first paragraph, "written description" (and not new matter).

Claims 1-32 and 48-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A) The specification broadly describes and the claims recite *"an agent which stimulates a CTLA4-associated apoptotic signal in the T cell" and "wherein the agent is an anti-CTLA monoclonal antibody"* as part of the invention.

However, applicant was not in possession of the claimed "agent" or anti-CTLA4 antibody" as an element of the claimed methods in the absence of providing sufficient structural and functional characteristics of the species or genus of such "agents" or "anti-CTLA4 antibodies" encompassed by the instant claim language, coupled with a known or disclosed correlation between function and structure.

While pages 8-20 of the instant specification sets forth anti-CTLA4 antibodies that simulate CTLA4-associated signals in T cells,

the appropriate epitope appears to limited as indicated in the Section on the Immunogen on pages 11-13 of the instant specification, as indicated on page 12 of the instant specification.

In a preferred embodiment, the CTLA4 epitope bound by the antibody comprises an amino acid sequence: (Xaa)n-Leu-Thr-Phe-Leu-Asp-Asp-(Xaa)n (SEQ ID NO: 33), wherein Xaa is any amino acid and n = 0-20, preferably 0-10, more preferably 0-5, most preferably 0-3. Thus, a peptide having the amino acid sequence of SEQ ID NO: 33 can be used as an immunogen. Accordingly, the invention further encompasses an isolated CTLA4 peptide comprising an amino acid sequence: (Xaa)n-Leu-Thr-Phe-Leu-Asp-Asp-(Xaa)n (SEQ ID NO: 33), wherein Xaa is any amino acid and n = 0-20.
Alternatively, it has been found that anti-CTLA4 antibodies capable of inducing apoptosis can cross-react with a number of other peptide sequences (determined by phage display technology as described in Example 3).

Examples of these other peptide sequences are shown on pages 12-13 of the instant specification.

The description of the instant specification indicates that both the ligand (i.e., anti-CTLA4 antibodies) and the epitope are important if not critical in achieving the appropriate claimed characteristic of "stimulating a CTLA4-associted apoptotic signal in T cells".

Not all anti-CTLA4 antibodies would have the appropriate claimed characteristic of "stimulating a CTLA4-associted apoptotic signal in T cells".

While pages 20-22 and 34-35 of the instant specification discloses that Other Agents that Induce T Cell Apoptosis can be determined,

the instant application has not provided a sufficient description showing possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus of Other Agents that Induce T Cell Apoptosis.

For example, with respect to CTLA4 ligands expressed on a B lymphoblastoid cell, Examples 4-5 on pages 44-49 of the instant specification discloses that the culture of activated T cell clones with t-DR7 in the presence of anti-CTLA4.1 antibodies suppressed proliferation and apoptosis.

However, no isolation of this putative CTLA-4 ligand is disclosed.

The Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d 1886,1895 (Fed. Cir. 2004).

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

The instant claims encompass in their breadth any "agent" or "anti-CTLA4 antibody" that are defined by a single or limited functional characteristic of "stimulating a CTLA4-associated apoptotic signal in the T cell" in the absence of structure.

Therefore, there is insufficient written description of the claimed genera of "agents" and "anti-CTLA4 antibodies" in the absence of defining the relevant identifying characteristics such as the structure or other physical and/or chemical characteristics of the claimed genus.

The specification broadly describes and the claims recite "an agent which stimulates a CTLA4-associated apoptotic signal in the T cell" and "wherein the agent is an anti-CTLA monoclonal antibody" as part of the invention.

B) In addition, the specification broadly describes and the claims recite *"administering to the subject at least one second agent that inhibits a costimulatory signal in the T cell", as it reads on "a blocking molecule that binds to a ligand selected from a group consisting of B7-1, B7-2 and CD28 (e.g., see claims 3-4).*

However, applicant was not in possession of the claimed "second agents" and "blocking molecules" as elements of the claimed methods in the absence of providing sufficient structural and functional characteristics of the species or genus of such "second agents" or "blocking molecules" encompassed by the instant claim language, coupled with a known or disclosed correlation between function and structure.

While page 24, paragraph 22 of the instant specification sets forth other "agents" and blocking molecules that also be administered to a subject,
the appropriate "agents" and "blocking molecules" appear to limited as indicated in the Section on Therapeutic Uses of CTLA4 Ligands that Induce T cell Apoptosis. on pages 22-24 of the instant specification, as indicated on page 24, paragraph 2 of the instant specification.

Additionally or alternatively, in order to induce apoptosis in a subject, it may also be beneficial to inhibit or prevent T cells from receiving a costimulatory signal in vivo, such as the costimulatory signal mediated by the interaction of CD28 with either B7-1 or B7-2. Accordingly, in addition to administering an agent that stimulates a CTLA4-associated apoptotic signal to a subject, another agent which inhibits generation of a costimulatory signal in T cells, such as a blocking molecule which binds to CD28, B7-1 or B7-2, may also be administered to the subject. Examples of suitable blocking molecules include an anti-CD28 Fab fragment, anti-B7-1 or anti-B7-2 blocking antibodies (i. e., antibodies which block CD28-B7-1/B7-2 interactions but do not induce a costimulatory signal in T cells) and soluble forms of CD28, B7-1 or B7-2 (e.g., immunoglobulin fusion proteins that block CD28-B7-1/B7-2 interactions but do not induce a costimulatory signal in T cells). Additionally, combinations of blocking molecules, e.g. an anti-B7-1 antibody and an anti-B7-2 antibody may be used.

The instant application has not provided a sufficient description showing possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus of at least one second agent that inhibits a costimulatory signal in the T cell", as it reads on "a blocking molecule that binds to a ligand selected from a group consisting of B7-1, By-2 and CD28.

For example, Coyle et al. (Nature Immunology 2: 203-209, 2001) (1449; #CK) disclose that B7-1 and B7-2 exhibit pronounced differences in structural and functional characteristics (page 204, column 1; The B7-1 and B7-2 Family) and disclose the increasing complexity in costimulatory signal regulating T cell function, wherein a number of molecules are poorly understood and likely have distinct roles in regulation T cells (see entire document).

Also, regarding clinical use of antibodies to CD28, it is noted that recent clinical trials of one such antibody, TGN1412, have resulted in "devastating effects," and a "damaging blow to the field" (see Wadman, Nature, 440: 388-389, 2006 and Hopkin, Nature 440: 855 – 856, 2006).

Further, as indicated above, The Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d 1886,1895 (Fed. Cir. 2004).

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

The instant claims encompass in their breadth any "second agent" or "blocking molecule" that are defined by a single or limited functional characteristic of "inhibiting a costimulatory signal in a T cell or binds to B7-1, B7-2 of CD28" in the absence of structure.

Therefore, there is insufficient written description of the claimed genera of "second agents" and "blocking molecules" in the absence of defining the relevant identifying characteristics such as the structure or other physical and/or chemical characteristics of the claimed genera.

Therefore, with respect to (A) and (B) above, the following is noted.

Further, the Court has interpreted 35 U.S.C. §112, first paragraph, to require the patent specification to "describe the claimed invention so that one skilled in the art can recognize what is claimed. Enzo Biochem, Inc. v. Gen-Probe Inc, 63 USPQ2d 1609 and 1618 (Fed. Cir. 2002). In evaluating whether a patentee has fulfilled this requirement, our standard is that the patent's "disclosure must allow one skilled in the art 'to visualize or recognize the identity of' the subject matter purportedly described." Id. (quoting Regents of Univ. of Cal. v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed Cir. 1997)).

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

It is not sufficient to define a genus without sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics.

In the absence of sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, the claimed invention is not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

The problem here is that the instant specification fails to provide a sufficient disclosure of

which "agents" or "anti-CTLA4 antibodies other than that addressed above" are required for the agent or anti-CTLA4 antibody to "stimulate a CTLA4-associated apoptotic signal in T cells" and

which "second agents that inhibit a costimulatory signal in the T cell", as it reads on "blocking molecules that bind to a ligand selected from a group consisting of B7-1, B7-2 and CD28".

in order "to induce apoptosis in an activated T cells in a subject, including in the treatment of autoimmunity", broadly encompassed by the claimed invention.

A skilled artisan cannot, as one can do with a fully described genera, visualize or recognize the identity of the members of the genus that exhibit this functional property.

Therefore, there is insufficient written description for genera of "agents" and "anti-CTLA4 antibodies" to "stimulate a CTLA4-associated apoptotic signal in T cells" in order "to induce apoptosis in an activated T cells in a subject, "second agents that inhibit a costimulatory signal in the T cell", as it reads on "blocking molecules that bind to a ligand selected from a group consisting of B7-1, B7-2 and CD28", including in the treatment of autoimmunity", broadly encompassed by the claimed invention at the time the invention was made and as disclosed in the specification as filed under the written description provision of 35 USC 112, first paragraph.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant has been reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

8. Claims 1-4 and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In evaluating the facts of the instant case, the following is noted:

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of Immunosuppressive drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations with the use of "agents" or "anti-CTLA4 antibodies that stimulate a CTLA4-associated apoptotic signal in T cells" and "second agents that inhibit a costimulatory signal in the T cell", as it reads on "blocking molecules that bind to a ligand selected from a group consisting of B7-1, B7-2 and CD28" can "induce apoptosis in an activated T cells in a subject, including in the treatment of autoimmunity", broadly encompassed by the claimed invention.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Kahan clearly states that no in vitro immune assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions (Cur. Opin. Immunol. 4: 553-560, 1992; see entire document, particularly page 558, column 2) (1449; #CF).

Blazar et al. (J. Immunol. 157: 3250-3259, 1996) (1449; #CE) disclose that anti-CD80 or anti-CD86 antibodies were ineffective in preventing T cell CD8-mediated GVHD lethality; that each antibodies was partially effective in CD4-mediated GVHD lethality and that the combination of anti-CD80 and anti-CD86 antibodies were effective in preventing GVHD lethality in murine experimental models (see entire document, including the Abstract)

Perrin et al. (J. Neuroimmunol. 65: 31-39,1996) (1449; #CI) disclose that in contrast to the effective treatment of disease with CTLA-4 Ig; anti-CD80 (B7-1) attenuated the first clinical disease episode but not the relapse, anti-CD86 (B7-2) had no significant effect on the course of disease, and the combined treatment with anti-CD80 plus anti-CD86 resulted in the exacerbation of disease (see entire document). It is also noted that CTLA-4 Ig had a marked but incomplete therapeutic effect in the EAE model.

In addition, Yi-qun et al. (Intl. Immunol. 8: 37-44, 1996) (1449; #CD) disclose that their findings have a number of important implications for therapeutic approaches (see entire document, particularly Discussion, last paragraph). It is clear that inhibition of T cell response to soluble antigens will require the blocking of both B7-2 and B7-1 to be effective. More, important it is unlikely that ongoing T cell response will be susceptible to inhibition by anti-B7 reagents, for example in autoimmune diseases.

Daikh et al. reviews The CD28-B7 Pathway and Its Role in Autoimmune Disease (J. Leukoc. Biol. 62: 156-162, 1997) (see entire document) discloses the confounding results and complexity of the Effects of Selective Blockade of B7-1 or B7-2 on Autoimmunity, including the exacerbation of diseases and the possible acceraltion of the development of autoimmunity with anti-CTLA4 antibodies (see pages 159-160).

Also, regarding clinical use of antibodies to CD28, it is noted that recent clinical trials of one such antibody, TGN1412, have resulted in "devastating effects," and a "damaging blow to the field" (see Wadman, Nature, 440: 388-389, 2006 and Hopkin, Nature, 440: 855 – 856, 2006).

Immunosuppression and inhibition of immune disorders are much easier to achieve under controlled in vitro conditions that experienced in the human immunoregulatory diseases targeted by the claimed invention. Further, in animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Therefore, it should be noted that although the animal models validate concepts based on studies of human disease, such studies are generally limited to the "acute" as opposed to "chronic" nature of the disease. Furthermore, autoimmunity reflects a memory response or antigen-experienced immune response.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective costimulatory-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting autoimmunity with the claimed "agents", anti-CTLA4 antibodies, second agents and blocking molecules" alone or in certain combinations.

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1 and 2 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4 and 8-11 of U.S. Patent No. 6,719,972.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims encompass methods which employ the anti-CTLA4 antibodies that anticipate the instant anti-CTLA-4 antibodies, including characteristics that stimulate CTLA4-associated signal in T cells recited in the instant.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to one another.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, Ph.D., J.D.
Primary Examiner
Technology Center 1600
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